UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,887	07/30/2001	Susanna M. Rybak	015280-325200US	5276

20350 7590 01/28/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
DECLOUX, AMY M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/28/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/918,887	RYBAK ET AL.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-26* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14 and 16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-12, 14 and 16-26 in Paper No. 9, filed 11-6-02, is acknowledged. The traversal is on the ground(s) that the two groups set forth by the Examiner stem from a common concept and theory, and therefore, it would not impose an undue burden to examine the claims together. This is not found persuasive because a search of a cytotoxic reagent and a search of a nucleic acid encoding a cytotoxic reagent are distinct for the reasons given in the restriction mailed 10-01-02 (Paper No. 8), and as such have acquired a separate status in the art because of their recognized divergent subject matter. MPEP 803 states that: "For the purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation, either separate classification, separate status in the art, or different field of search. Because Group I and Group II have distinct classifications, and because a search in the non-patent literature of Group I would not be co-extensive with a search of Group II, an examination and search of both Groups I and II in a single application would constitute a serious undue burden on the Examiner, and therefore, restriction for examination purposes as indicated is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9, filed 11-6-02.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Specifically reference to parent application 09/071,672, US Patent 6,395,276, is required.

Specification

The disclosure is objected to because of the following informalities:

A) page 4, lines 10-11 disclose "a method selectively". Perhaps the word "of" was intended to be inserted between the word "method" and the word "selectively".

B) page 29, line 8 discloses a "[]" before the beginning of the second sentence on line 8.

Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Specifically, an embedded hyperlink is disclosed on page 2, line 30.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically claim 14 is indefinite in the recitation of the phrase "recombinant fusion" because it is not clear what said phrase means and said phrase is not defined in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6-12, 14, 16, 18 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a selective cytotoxic reagent comprising an onc protein having measurable ribonucleolytic activity covalently linked to an antibody directed against a surface marker specific to a B cell, wherein the cytotoxic reagent is at least 100 times more cytotoxic to target cells bearing a B cell marker than a comparison reagent comprised of the same antibody joined to the human non-toxic Rnase eosinophil-derived neurotoxin (EDN), and a pharmaceutical composition thereof.

The instant disclosure of a selective cytotoxic reagent comprising an onc protein identified by the amino acid sequences of SEQ ID NO:s 1 and 3, (the latter sequence being encoded by SEQ ID NO:2), derived from Rana pipiens, does not adequately describe the scope of the claimed genus of onc proteins having measurable ribonucleolytic activity, comprised by the recited reagent. The specification does not describe a selective cytotoxic reagent comprising an onc protein from any species other than Rana pipiens, and therefore, the invention encompassing a selective cytotoxic reagent comprising an onc protein derived from all species is not adequately described. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Though the instant claims encompass a protein, the principle isd the same. It is noted that a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*

Claims 1, 3, 6-12, 14, 16, 18 and 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for onc proteins having the amino acid sequence of SEQ ID NO:1 and SEQ ID NO:3, encoded by SEQ ID NO:2, which are encompassed by claims 28, 30 and 31, respectively, does not reasonably provide enablement for any onc protein other than those with measurable ribonucleolytic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant disclosure of a selective cytotoxic reagent comprising an onc protein derived ONLY from Rana pipiens, does not provide sufficient guidance and direction regarding making selective cytotoxic reagent comprising an onc protein derived from any species other than Rana pipiens. The state of the art does not teach a selective cytotoxic reagent comprising an onc protein wherein the cytotoxic reagent is at least 100 times more cytotoxic to target cells bearing a B cell marker than a comparison reagent comprised of the same antibody joined to the human non-toxic Rnase eosinophil-derived neurotoxin (EDN). Rybak, S. et al., (Tumor Targeting, 1:141-147, 1995) (BR PTO-1449)), teach that though onc Rnase isolated from Rama pipiens embryos and eggs has anti-tumor activity while , unlike human RNAses ANG and EDN (see entire article, including page 141. Therefore it would require undue experimentation for one of skill in the art to make a selective cytotoxic reagent comprising an onc protein other than one derived from Rana pipiens, having the amino acid sequence of SEQ ID NO:1 and SEQ

ID NO:3, encoded by SEQ ID NO:2 without further guidance and direction from the specification. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, onc proteins would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 102

Rejection under 35 U.S.C 102(e), Patent Application Publication or Patent to Another with Earlier Filing Date, in view of the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 9-11, 14, 16, 18, 21-22 and 25-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Goldenberg (US Patent #6,083,477).

The '477 patent teaches a method where the monoclonal antibodies LL1 and LL2 that recognize CD74 (invariant chain) and CD 22, respectively were conjugated to the RNAse EDN or onconase in a pharmaceutical composition, in a method of killing cell lines that express Class II invariant chain and CD22 (see entire patent, especially in Example 2 in column 7, Example 8 in column 12 and Table 2). Furthermore, said Table 2 shows that the onc cytotoxic reagent attached to the LL2 antibody is at least 100 times more cytotoxic compared to the same antibody attached to EDN. Therefore, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 14, and 16-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rybak et al. (U.S. Patent No. 5,840,840) AND/OR Ghetie et al. (Cancer Research 51:5876-5880, 1991)(BF, PTO-1449), in view of Rybak, S. et al., (Tumor Targeting, 1:141-147, 1995) (BR PTO-1449), in view of Rybak et al. (PNAS 89:3165-3169, 1992), in view of Goldenberg (US Patent #6,083,477), in view of Sausville et al (Blood 85 (12):3457-3465 (1995)), (BT IDS), in view of Janeway et al, Immunolobiology, 3rd edition, Current Biology Ltd, London, England 1997 pages 13:7-8, and in view of Huston et al. (PNAS (1988) 85:5879-5883).

The instant claims are drawn to a selective cytotoxic reagent comprising an onc protein having measurable ribonucleolytic activity covalently linked to an antibody directed against a surface marker specific to a B cell, wherein the cytotoxic reagent is at least 100 times more cytotoxic to target cells bearing a B cell marker than a comparison reagent comprised of the same antibody joined to the human non-toxic Rnase eosinophil-derived neurotoxin (EDN), and a pharmaceutical composition thereof.

('840) teaches treatment methods involving the use of a pharmaceutical composition comprising the cytotoxic reagent which comprises an RNase linked to a recognition moiety that binds a specific cell marker, and which, upon binding to a cell surface marker, kills the cell. (See entire article, in particular the Abstract). The specification of the instant application 09/071672 teaches that "onc protein" refers to an RNase A from *Rana pipiens* (see entire specification, especially pages 9 and 17).

('840) differs from the claims which encompass a recombinant RNase having the amino acid sequence of SEQ ID NO:1 or SEQ ID NO: 3, encoded by SEQ ID NO:2, nor does ('840) teach the B cell marker CD22 specifically, which is encompassed by claim 32.

Ghetie et al. (BF) teach a method of killing Daudi cells which are derived from human Burkitt B cell lymphomas, using an immunotoxin comprised of an antibody fragment of a murine monoclonal anti-CD22 antibody RFB4 chemically linked to the toxin ricin A chain (see entire article, especially page 5876, paragraphs one and two of the Introduction). Ghetie et al. differ from the claims in that the toxic moiety of the immunotoxin is not an onc protein.

Sausville et al teach an immunotoxin comprising the monoclonal anti-CD22 antibody to ricin A (see entire article, including page 3457, column 1).

Rybak et al. ('95) teach Onconase, a monomeric homolog of RNaseA, isolated from *Rana pipiens*, that has anti-tumor effects, (see entire article, especially page 141, Introduction, lines 8-11).

Rybak et al ('92) teaches a chimeric gene encoding an antibody directed to the human transferrin receptor, and that the antibody gene is fused to the gene for angiogen which encodes a human homolog of pancreatic RNase, and that this recombinant immunotoxin is cytotoxic to tumor cells bearing the transferrin receptor (see entire article, especially the Abstract on page 3165).

Goldenberg teaches as above.

Janeway et al teaches standard techniques in the art at the time the invention was made including that humanized antibodies comprise the CDRs of a mouse monoclonal antibody onto the human framework of a human immunoglobulin, and that said chimeric antibodies are far less immunogenic in humans than the parent mouse monoclonal antibodies.

Huston et al teach the advantages of single chain monoclonal antibodies that retain the same CDR regions and specificity as the parent monoclonal antibody, but display reduced immunogenicity and accelerated pharmacokinetics (see entire article, including page 5883, column 1, last paragraph).

Accordingly, one of ordinary skill in the art at the time the invention was made, would have been motivated to kill malignant B cells such as human Burkitt lymphoma cells with methods that used a pharmaceutical composition that comprised an immunotoxin comprising a B cell specific antibody directed against the B cell surface marker CD22 that was linked to a toxin which was cytotoxic to human Burkitt lymphoma cells as taught by Ghetie, such as RFB4 taught by Sausville et al, or LL2 taught by Godenberg, and would have substituted the Onconase toxin given its cytotoxic properties as taught by Rybak et al, ('95), in place of the ricin toxin that comprised the toxin portion of the immunotoxin taught by Ghetie. Furthermore, one would have been motivated to produce the onc protein toxin recombinantly using the methods taught by Rybak et al. ('92) of producing an immunotoxin which comprises a recombinantly produced human RNase toxin connected to an antibody, since said immunotoxin was cytotoxic to tumor cells bearing the cell surface marker to which the antibody was directed. Furthermore, one would have been motivated to have made and used said immunotoxin comprising humanized monoclonal antibodies because Janeway et al teaches their reduced immunogenicity. Similarly one would have been motivated to have

used said immunotoxin comprising single chain monoclonal antibodies because Huston et al teaches their reduced immunogenicity and increased pharmacokinteics.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 872-9306 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.
Patent Examiner,
Group 1640
January 27, 2003

Amy DeCloux
1-27-03